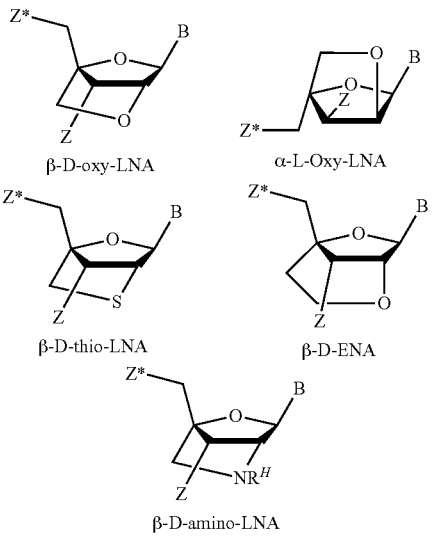
[0117] Specifically preferred LNA units are shown in scheme 2:

Scheme 2



[0118] The term "thio-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above is selected from S or —CH_2—S—. Thio-LNA can be in both beta-D and alpha-L-configuration.

[0119] The term "amino-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above is selected from —N(H)—, N(R)—, CH_2—N(H)—, and —CH_2—N(R)—where R is selected from hydrogen and C_{1-4}-alkyl. Amino-LNA can be in both beta-D and alpha-L-configuration.

[0120] The term "oxy-LNA" comprises a locked nucleotide in which at least one of X or Y in the general formula above represents —O— or —CH_2—O—. Oxy-LNA can be in both beta-D and alpha-L-configuration.

[0121] The term "ena-LNA" comprises a locked nucleotide in which Y in the general formula above is —CH_2—O— (where the oxygen atom of —CH_2—O— is attached to the 2'-position relative to the base B).

[0122] LNAs are described in additional detail herein.

[0123] One or more substituted sugar moieties can also be included, e.g., one of the following at the 2' position: OH, SH, SCH_3, F, OCN, OCH_3 OCH_3, OCH_3 $O(CH_2)$n CH_3, $O(CH_2)$n NH_2 or $O(CH_2)$n CH_3 where n is from 1 to about 10; C1 to C10 lower alkyl, alkoxyalkoxy, substituted lower alkyl, alkaryl or aralkyl; Cl; Br; CN; CF_3; OCF_3; O—, S—, or N-alkyl; O—, S—, or N-alkenyl; $SOCH_3$; SO_2 CH_3; ONO_2; NO_2, N_3; NH2; heterocycloalkyl; heterocycloalkaryl; amino alkylamino; polyalkylamino; substituted silyl; an RNA cleaving group; a reporter group; an intercalator; a group for improving the pharmacokinetic properties of an oligonucleotide; or a group for improving the pharmacodynamic properties of an oligonucleotide and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy [2'-O—$CH_2CH_2OCH_3$, also known as 2'-O-(2-methoxyethyl)](Martin et al, Helv. Chim. Acta, 1995, 78, 486). Other preferred modifications include 2'-methoxy (2'-O—CH_3), 2'-propoxy (2'-OCH_2 CH_2CH_3) and 2'-fluoro (2'-F). Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyls in place of the pentofuranosyl group.

[0124] Single stranded oligonucleotides can also include, additionally or alternatively, nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include adenine (A), guanine (G), thymine (T), cytosine (C) and uracil (U). Modified nucleobases include nucleobases found only infrequently or transiently in natural nucleic acids, e.g., hypoxanthine, 6-methyladenine, 5-Me pyrimidines, particularly 5-methylcytosine (also referred to as 5-methyl-2' deoxycytosine and often referred to in the art as 5-Me-C), 5-hydroxymethylcytosine (HMC), glycosyl HMC and gentobiosyl HMC, isocytosine, pseudoisocytosine, as well as synthetic nucleobases, e.g., 2-aminoadenine, 2-(methylamino)adenine, 2-(imidazolylalkyl)adenine, 2-(aminoalklyamino)adenine or other heterosubstituted alkyladenines, 2-thiouracil, 2-thiothymine, 5-bromouracil, 5-hydroxymethyluracil, 5-propynyluracil, 8-azaguanine, 7-deazaguanine, N6 (6-aminohexyl)adenine, 6-aminopurine, 2-aminopurine, 2-chloro-6-aminopurine and 2,6-diaminopurine or other diaminopurines. See, e.g., Kornberg, "DNA Replication," W. H. Freeman & Co., San Francisco, 1980, pp 75-77; and Gebeyehu, G., et al. Nucl. Acids Res., 15:4513 (1987)). A "universal" base known in the art, e.g., inosine, can also be included. 5-Me-C substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2° C. (Sanghvi, in Crooke, and Lebleu, eds., Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and may be used as base substitutions.

[0125] It is not necessary for all positions in a given oligonucleotide to be uniformly modified, and in fact more than one of the modifications described herein may be incorporated in a single oligonucleotide or even at within a single nucleoside within an oligonucleotide.

[0126] In some embodiments, both a sugar and an internucleoside linkage, i.e., the backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, for example, an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos. 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al, Science, 1991, 254, 1497-1500.

[0127] Single stranded oligonucleotides can also include one or more nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases comprise the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases comprise other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other